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Invited article

Disruption of iron homeostasis and resultant health effects upon exposure to various environmental pollutants: A critical review

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ABSTRACT

Environmental pollution has become one of the greatest problems in the world, and the concerns about environmental pollutants released by human activities from agriculture and industrial production have been continuously increasing. Although intense efforts have been made to understand the health effects of environmental pollutants, most studies have only focused on direct toxic effects and failed to simultaneously evaluate the long-term adaptive, compensatory and secondary impacts on health. Burgeoning evidence suggests that environmental pollutants may directly or indirectly give rise to disordered element homeostasis, such as for iron. It is crucially important to maintain concerted cellular and systemic iron metabolism. Otherwise, disordered iron metabolism would lead to cytotoxicity and increased risk for various diseases, including cancers. Thus, study on the effects of environmental pollutants upon iron homeostasis is urgently needed. In this review, we recapitulate the available findings on the direct or indirect impacts of environmental pollutants, including persistent organic pollutants (POPs), heavy metals and pesticides, on iron homeostasis and associated adverse health problems. In view of the unanswered questions, more efforts are warranted to investigate the disruptive effects of environmental pollutants on iron homeostasis and consequent toxicities.

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Introduction

Nowadays, ca. 24% of diseases and 23% of the deaths of human beings can be attributed to environmental factors, based on the world health organization (WHO) report (WHO, 2006), in which environmental pollutants emerge as the greatest danger to public health. Although epidemiological

studies have provided a great deal of evidence on the relationship between environmental pollutants and diseases, the pathogenic effects of environmental pollutants have not been fully understood due to their complicated biological activities. Upon exposure, the human body will adapt or implement numerous pathways to compensate for alterations induced by environmental pollutants. To reveal

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these underlying pathogenic mechanisms, numerous *in vitro* and *in vivo* studies have been carried out to gain knowledge about the exposure risk of environmental pollutants and their health effects.

In terms of health effects of environmental pollutants, some aspects should be carefully and systematically considered. (1) The effects of environmental pollutants on disease initiation are more likely to be indirect rather than direct (Porta, 2006). For example, it was reported that persistent organic pollutants (POPs) in adipose tissue indirectly influenced breast cancer development and/or progression (Reaves et al., 2015). (2) The exposure conditions of pollutants in the natural environment and human body are complicated. Environmental factors, individual conditions, and interactions of multiple pollutants should be considered. Moreover, the exposures to pollutants are life-course environmental exposures, referred to as the exposome (Lioy and Rappaport, 2011), and both internal and external factors contribute to environmental pollutant-induced health effects. (3) Environmental pollutants could possibly induce or enhance the initiation and/or development of various diseases through epigenetic changes, including DNA methylation, histone modification and non-coding RNA mediated mechanisms (Hou et al., 2012; Vaiserman, 2014). It has been reported that polychlorinated biphenyls (PCBs) have the ability to activate androgen receptor (AR) transcriptional activity, and this action is assisted by the histone demethylase Jarid1b (Casati et al., 2013). (4) Environmental pollutants can cause metabolic disruption in the human body, such as with iron metabolism, resulting in significant health risk (Casals-Casas and Desvergne, 2011).

Iron is a necessary chemical element, involved in a wide spectrum of fundamental biological processes, such as DNA replication, iron–sulfur synthesis, and energy metabolism (Torti and Torti, 2013). Iron homeostasis is concertedly governed under normal settings, and disordered iron metabolism can lead to a wide array of diseases, including cancers. Misregulation of intracellular iron metabolism has been demonstrated to contribute to malignant phenotypes in tumors. Clinical studies also reported that excessive body iron burden could increase the risk of tumor occurrence (Torti and Torti, 2013; Y. Yu et al., 2007). Excess iron could accelerate tumor initiation and progression by enhancing the formation of free radicals, and by functioning as a necessary nutrient that fosters tumor cell proliferation as well (Torti and Torti, 2013). Moreover, recent studies by our group and others demonstrated that environmental pollutants, including PCBs, cadmium (Cd) and chlorpyrifos (CPF), could alter the expression levels of hepcidin (the central regulator of iron absorption) and ferroportin (FPN, the only regulator of iron exportation), and thus disrupt the hepcidin-FPN signaling (Qian et al., 2015; Sun et al., 2014, 2015; L. Wang et al., 2013a). Finally, it should be stressed that the effect of pollutant-induced disruption to iron homeostasis could be a long-term and secondary event; however, it also occurs as an acute and direct one. For example, we demonstrated that PCB-77 exposure in mice could consistently repress hepatic hepcidin expression by more than 65% at 6, 12, and 24 hr, compared with untreated mice. Similarly, alterations of FPN were also found with cadmium and CPF after a short time exposure. These preliminary data suggest that environmental pollutants have the potential to directly disorder iron homeostasis, which warrants careful attention in future studies.

In the current review, we recapitulate the potential detrimental effects of environmental pollutants on iron metabolism, and highlight the corresponding mechanisms responsible for cellular responses (Table 1). The improved understanding of environmental pollutant-mediated imbalance of iron metabolism will assist in elucidating their potential adverse effects on health.

1. Iron homeostasis and health effects

Iron is an essential biometal necessary for most forms of life. Iron plays a crucial role in various biological processes, because it is a necessary component of iron-containing proteins, including enzymes responsible for DNA replication and repair, cell cycle control, and mitochondrial energy metabolism (Duce et al., 2010; Ganeshaguru et al., 1980). Iron also contributes to cellular signaling, such as in cell survival and inflammation (Xiong et al., 2014). However, excessive iron has the potential to induce adverse effects on human health, due to its ability to gain and lose electrons, to participate in redox cycling and to generate free-radical species (Torti and Torti, 2013). The Fenton reaction is the major route responsible for iron-induced radical production. In this chemical reaction, ferrous iron reacts with hydrogen peroxide to produce $\cdot\text{OH}$ radical by donating an electron ($\text{Fe}^{2+} + \text{H}_2\text{O}_2 \rightarrow \text{Fe}^{3+} + \cdot\text{OH} + ^-\text{OH}$). Therefore, excessive iron generates increased radical species, resulting in oxidative damage to DNA, lipids and proteins (Dizdaroglu et al., 1991; Inoue and Kawanishi, 1987).

To balance the absorption, transport, storage and utilization of iron in the body, systemic iron homeostasis is fine-tuned through various signaling pathways. The disruption of cellular signaling for iron homeostasis can cause iron deficiency or iron overload, which are deleterious to health. On one hand, iron deficiency can incur anemia, which is a major issue of public health for children and pregnant woman, especially for those in low- and middle-income countries (Pasricha et al., 2013). On the other hand, excess iron burden is considered to contribute to a wide spectrum of cancer types including breast cancer, lung cancer, prostate cancer, gastrointestinal cancer, hepatocellular cancer, and hematological malignancies (Torti and Torti, 2013; Zhang and Zhang, 2015). Greatly increased risk of hepatocellular, colorectal and breast cancers has been observed in hereditary hemochromatosis patients (HFE C282Y homozygotes) with iron overload, compared to individuals without the HFE variant (Osborne et al., 2010).

Hepcidin-FPN signaling is one of the key mechanisms responsible for iron supply, utilization, recycling and storage. Hepcidin, a 25 amino acid peptide, is mainly derived from hepatocytes, and it fundamentally equilibrates systemic iron homeostasis. The expression of hepcidin is primarily regulated by iron status, hypoxia, anemia and inflammation (Ganz, 2013). FPN is the only known iron exporter in mammals, and its concentration is mainly controlled by the binding of hepcidin. Our recent studies demonstrated that, following exposure to environmental pollutants, the hepcidin-FPN axis is misregulated in administrated animals along with disordered systemic iron homeostasis, which will be discussed in more detail in the following sections.

2. Effects of organic pollutants on iron homeostasis

2.1. Mechanisms underlying organic pollutants' effects on iron homeostasis

Considering the potential mechanisms, the following pathways are considered. First, organic pollutant exposure was found to elevate the concentration of heme oxygenase-1 (HO-1), a key enzyme involved in modulation of oxidative injury and the recycling of red blood cells for iron utilization (Elbirt and Bonkovsky, 1999). Excess HO-1 might give rise to excessive iron, as a result of the degradation of heme (Lee et al., 2006). Second, the functions of iron-related proteins such as transferrin receptor (TfR) and ferritin could be disturbed by organic pollutant exposure (such as PCBs) through alteration of gene transcription and protein synthesis (Santamaria et al., 2011). Third, a functional estrogen response element (ERE) in the promoter of hepcidin gene was previously verified by

our research group, and its expression could be regulated by estrogen (Hou et al., 2012). Analogous to natural estrogen, PCB family members (such as PCB 126 and 153) exhibit estrogenic activity, which determines their ability to disrupt systemic iron metabolism (Qian et al., 2015). At present, the mechanisms responsible for organic pollutant-induced effects on iron homeostasis are still elusive, and more mechanistic studies are warranted.

2.2. Persistent organic pollutants (POPs)

Previous studies demonstrated an alteration to iron metabolism in response to POPs (Smith et al., 1995; Whysner and Wang, 2001). Although the interactions of POPs with receptor molecules appear to play an important role in their toxicity (Sorg, 2014), they are not the only pathway through which POPs exert adverse effects. Our recent studies revealed that PCBs could disrupt systemic iron homeostasis, resulting in detrimental effects on animals. However, our understanding

Table 1 – Disruption of iron homeostasis and resultant health effects induced by environmental pollutants.

Environmental pollutants	Impacts on iron metabolism	Mechanisms	Potential diseases associated with iron disorders	Reference
Organic pollutants	PCBs Iron overload	HO-1 over-expression	Cognitive and motor neurobehavioral abnormalities	Lee et al. (2006)
	Iron overload	Estrogenic activity mediated by ERE	Breast cancer	Qian et al. (2015), Wang et al. (2013a)
	DDT Iron utility impairment	Hepcidin up-regulation induced by interleukin-6	Anemia	Tomita et al. (2013)
	CPF Cellular iron depletion	FPN and hepcidin expression changes	–	Sun et al. (2014)
Heavy metals	Cd Decreased iron absorption	Competition with iron uptake	Anemia	Hamilton and Valberg (1974)
	Excess iron release	Induction of the FPN expression by ROS; enhancing FPN translation via iron responsive element	–	Park and Chung (2009), Sun et al. (2015)
	Iron overload	Decreased erythropoietin synthesis	Itai-itai disease associated renal anemia	Horiguchi et al. (2011), Horiguchi et al. (1994)
	Pb –	Inhibition of pyrimidine 5'-nucleotidase	Hemolysis	Lachant et al. (1984)
	–	Inhibition of enzymes involved in heme biosynthesis	Anemia	Moore et al. (1987)
	As Iron deposition	Erythrophagocytosis	Kidney damage	Kwon et al. (2015)
	–	Inhibition of pyruvate dehydrogenase	Anemia	Shen et al. (2013a), Ye and Rouault (2010)
	–	Nrf2 activation and subsequent HO-1 induction	–	Abiko et al. (2010), Li et al. (2013)
	Iron depletion	Activated binding of IRP-1 to IRE	–	Li et al. (2006)
	Decreased iron in brain	–	Neurological and neuro developmental disorders	Wang et al. (2013b)
	Cu –	Function as prothetic groups to facilitate iron metabolism	–	Prohaska (2011)
	Iron depletion	Activated binding of IRP-1 to IRE	–	Li et al. (2006)
	Increased uptake and transport of iron	Up-regulation of DMT1, FPN-1, and hephaestin	–	Han and Wessling-Resnick (2002)

Dash (–) indicates not identified or repo; PCBs: polychlorinated biphenyls; DDT: Dichloro-Diphenyl-Trichloroethane; CPF: chlorpyrifos; Cd: cadmium; Pb: lead; As: Arsenic; Cu: Copper; HO-1: heme oxygenase-1; ERE: estrogen response element; FPN: ferroportin; ROS: reactive oxygen species; Nrf2: nuclear factor-E2-related factor 2; IRP1: iron-regulatory protein 1; IRE: iron response element; DMT-1: divalent metal transporter-1.

of the relationship between POP exposure and iron homeostasis is still limited and urgently needs to be strengthened.

2.2.1. Polychlorinated biphenyls

PCBs, the representative POPs, have received enormous attention for a long time (Vested et al., 2014). Previous studies have mainly focused on their reproductive toxicity (Sha et al., 2015), neurotoxicity (Kodavanti and Tilson, 1997), immunotoxicity (Smialowicz et al., 1989), endocrine-interference effects (Yang et al., 2008) and oncogenicity (Lucena et al., 2001; Wolff et al., 2000). However, their potential influence on element metabolism remains largely unknown. In a previous study by our research group, we found that the expression of hepcidin could be inhibited in HepG2 and L-02 hepatocytes upon exposure to PCB-77 (L. Wang et al., 2013a). Inhibition by PCB-77 on hepcidin expression levels was further confirmed in mice, associated with increase of serum iron content and reduction of splenic iron content (L. Wang et al., 2013a). Furthermore, our recent study further demonstrated that PCB126 and PCB153 repressed the expression of hepcidin in the liver through estrogen-like effects (Qian et al., 2015). Due to its stronger estrogenic activity, PCB126 caused greater repression than PCB153 (Qian et al., 2015). These preliminary data suggested that PCB exposure might disturb iron metabolism and influence systemic iron homeostasis (Fig. 1), resulting in enforced iron supply to other tissues including tumors. Excessive iron availability will enhance the rate of iron-dependent biological processes necessary for cell growth, and elevate the risk of genetic mutation via free radical production (Bystrom et al., 2014; Torti and Torti, 2011). It has been suggested that excessive iron can greatly increase the incidence of various cancers and neurological diseases (Ganz and Nemeth, 2011; Zhang et al., 2014). Additionally, numerous studies have suggested the notable contribution of excess iron to tumor development (Bystrom et al., 2014; Richardson et al., 2009; Torti and Torti, 2011).

Because of their chemical structure similarity to PCBs, other types of POPs (dioxin-like compounds) including beta-hexachlorocyclohexane (HCH), dichloro-diphenyl-trichloroethane (DDT) and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) that exhibit estrogenic activity may be capable of affecting iron homeostasis. However, this likelihood has not yet been investigated, but it is worth close scrutiny. The improved understanding of POP-induced effects on iron homeostasis will be of great help in elucidating the mechanisms responsible for POP-associated disorders.

2.2.2. Dichloro-diphenyl-trichloroethane

DDT constitutes another well-known group of POPs, widely used as pesticides in the past (Davies, 2006; Wang et al., 2009). A number of studies suggested that exposure to DDT and its derivatives was implicated in various disorders including weight loss, anorexia and anemia (Turusov et al., 2002). An epidemiological research study reported that the aplastic anemia was associated with exposure to chemicals such as DDT (Issaragrisil et al., 2006). Mariko Tomita and colleagues also demonstrated that DDT might undermine the hematopoietic system, leading to microcytic anemia (Tomita et al., 2013). Moreover, it was found that long-term administration of p,p'-DDT induced significant inflammation anemia and microcytic anemia in rats in a dose-dependent manner (Tomita et al., 2013), which could possibly result from the impairment of iron utilization during erythropoiesis.

2.3. Organophosphate pesticides (OPs)

CPF is one of the most widely produced and commonly used OPs, and CPF contamination in fruits and vegetables is serious (Gebremariam et al., 2012; Singh et al., 2002; Zhao et al., 2014). A number of studies have documented the adverse

Fig. 1 – A schematic for PCB-induced effects on iron homeostasis. An inhibitory effect of PCBs was identified on suppressing the expression of hepcidin through estrogen-like activity and thus altering systemic iron metabolism. This is a reproduction with minor modifications from our previous paper (Qian et al., 2015). PCBs: polychlorinated biphenyls; Hep: hepcidin; FPN: ferroportin; ERE: estrogen response element; ER: estrogen receptor; TSS: transcription start site.

health effects of CPF, such as hepatotoxicity, neurotoxicity and endocrine disruption (Mink et al., 2012; Ridano et al., 2012; Singh et al., 2011). Our recent study revealed a novel toxic feature of CPF through disturbance of cellular iron homeostasis, as illustrated in Fig. 2 (Sun et al., 2014). CPF can greatly enhance the expression levels of FPN in macrophages (Sun et al., 2014), but diminish the expression of hepcidin in hepatocytes. Therefore, CPF exposure depleted the storage of iron in cells, evidenced by the reduction of the labile iron pool (LIP) in both macrophages and hepatocytes (Sun et al., 2014).

3. Effects of heavy metals on iron homeostasis

Compared to organic pollutants, heavy metals are more universal and more easily exposed to humans through environmental and occupational routes (Y. Li et al., 2006; Khan et al., 2013; Zhou et al., 2014). The adverse health effects of heavy metals have long been known from previous investigations (Järup, 2003). For example, some heavy metals such as Cd, lead (Pb), mercury (Hg) and arsenic (As) are of great concern because of their pronounced toxicity (Järup, 2003; Tchounwou et al., 2012). These heavy metals are systemic toxicants and could induce damages to multiple organs (Tchounwou et al., 2012), including the kidney (Kim et al., 2015), liver (R.A. Yu et al., 2007), lung (Rokadia and Agarwal, 2013), heart (Agarwal et al., 2011), bone (Staessen et al., 1999) and skin (Hunt et al., 2014). Once these heavy metals enter the body, they bind to proteins that contain sulfhydryl groups (e.g., glutathione), due to their electrophilic properties. Depletion of glutathione will increase intracellular oxidative stress (Solenkova et al., 2014), which further induces lipid peroxidation, protein oxidation, DNA oxidation and other toxic effects (Solenkova et al., 2014). Moreover, heavy metals can bind to nitrogen- and oxygen-containing groups or compete with the essential metal ions in enzyme molecules, and thus cause conformational and functional changes of these biomolecules and thereby disturb the *in vivo* metal homeostasis (Koedrich and

Seo, 2011). Since iron is an essential element, the alterations of its homeostasis in response to heavy metals should be critically considered.

3.1. Mechanisms responsible for the disruption of iron homeostasis induced by heavy metals

Although previous studies have revealed the toxicity of heavy metals in eliciting iron and red blood cell disorders, the molecular mechanisms are incompletely understood. Heavy metals (e.g. Cd and Hg) could affect iron homeostasis through two major pathways, namely directly competing with iron ions in biomolecules and indirectly generating oxidative stress. As previously recognized, iron is mostly bonded in the center of a large heterocyclic organic ring called porphyrin. However, according to the Irving–Williams series ($Zn^{2+} < Cu^{+} > Cu^{2+} > Ni^{2+} > Co^{2+} > Fe^{2+} > Mn^{2+} > Mg^{2+} > Ca^{2+}$), Fe^{2+} in the heme group could be replaced by other metal ions with a higher affinity. In this way, the heavy metals are able to disturb the balance of the intracellular iron pool by competing with iron transporters or iron-regulated enzymes, such as transferrin, divalent metal transporter 1 (DMT-1) and iron-regulatory proteins (IRPs) (Q. Li et al., 2006). Meanwhile, heavy metals could generate free radicals, such as reactive oxygen species (ROS), through binding with glutathione (Solenkova et al., 2014) and metallothionein (MT) (Sato and Kondoh, 2002), thus driving oxidative stress and incurring detrimental effects on cells (Farina et al., 2013). Thereby, the following events may occur to break concerted iron balance. First, the up-regulation of antioxidant HO-1 will trigger the degradation of heme, and the resultant free iron may aggravate the oxidative stress and cause damage to mitochondria and other organelles (Zhang and Piantadosi, 1992). Second, the activation of some transcriptional factors, e.g. nuclear factor-E2-related factor 2 (Nrf2), would alter cellular iron status through promoting transcription of iron-related genes, such as ferritin (Huang et al., 2013) and FPN (Y. Chen et al., 2015).

Fig. 2 – A proposed mechanism responsible for CPF-mediated disruption to cellular iron metabolism in macrophages and hepatocytes. CPF at sublethal concentrations confounds cellular iron metabolism by elevating FPN expression in macrophages and suppressing hepcidin expression in hepatocytes. This is a reproduction with minor modifications from our previous paper (Sun et al., 2014). CPF: chlorpyrifos; Hep: hepcidin; FPN: ferroportin; TSS: transcription start site.

3.2. Cadmium (Cd)

After entering the body, Cd can easily react with thiol groups and substitute for zinc (Zn) in enzymes necessary for critical metabolic processes (Gena et al., 2010). Renal and skeletal systems are the primary sites for Cd accumulation (Gena et al., 2010; Satarug et al., 2010). It is estimated that approximately 50% of total Cd in the body is accumulated in the kidney, and a dose-dependent response could be observed between urinary Cd levels and the concentration of N-acetyl- β -D-glucosaminidase (U-NAG), a biomarker of early kidney damage (Gena et al., 2010; Thomas et al., 2009).

It is well-known that chronic Cd poisoning can incur anemia through three pathways including hemolysis (Kunimoto et al., 1985), iron insufficiency (Hamilton and Valberg, 1974) and decreased production of erythropoietin (Horiguchi et al., 1994, 2010). Cd exerted direct damage to red blood cells at the very beginning of exposure by destroying cytoskeletons and causing deformability of cell membranes (Horiguchi, 2007). Meanwhile, oral Cd exposure caused iron deficiency in animals (Stonard and Webb, 1976), suggesting Cd could compete with iron uptake in the intestine (Hamilton and Valberg, 1974). By contrast, increased systemic iron content, associated with anemia, occurred in those who were exposed through routes other than the alimentary tract, or those with itai-itai disease (Horiguchi, 2007; Horiguchi et al., 1994, 2010; Koji et al., 1984; Stonard and Webb, 1976). It is thus reasonable to assume that Cd could disturb systemic iron balance during erythropoiesis. After long-term Cd exposure, renal anemia known as itai-itai disease can be observed at the ultimate stage along with reduced production of erythropoietin.

It has been suggested that Cd induces the expression of FPN-1 in macrophages through ROS production (Park and Chung, 2009). In enterocytes, excessive Cd enhanced the expression of DMT-1 (Gunshin et al., 1997). Meanwhile, Cd can impair erythropoietin synthesis in the kidney, resulting in an increase in hepcidin production and reduction of iron availability for erythropoiesis (Horiguchi, 2007). Our recent study found the expression levels of FPN could be up-regulated in macrophages upon exposure to sublethal Cd, and LIP was diminished (Sun et al., 2015). In another study by our group, we demonstrated that Cd could likely compete with ferrous iron to interact with the 5'-UTR iron response element of FPN's mRNA, affecting the translation of FPN (Sun et al., 2015). Additionally, it has been suggested that Cd may regulate hepcidin-mediated iron homeostasis by inducing the secretion of IL-6 (Horiguchi et al., 2011).

3.3. Lead (Pb)

As a neurological developmental toxicant, Pb substitutes for calcium (Ca) and Zn in enzymes, leading to calmodulin-dependent disorders and neurotransmitter disturbances (Mason et al., 2014). Moreover, Pb can exert adverse effects on hematological, renal and gastrointestinal systems (Chen et al., 2013). It has been suggested that Pb poisoning could cause anemia through: (a) reducing heme contents (Alexander et al., 1998; Lachant et al., 1984; Moore et al., 1987; Oskarsson and Fowler, 1985), (b) inhibiting the activity of erythrocyte pyrimidine 5'-nucleotidase (Valentine et al., 1976), and (c) triggering phosphatidylserine externalization on red blood cells and

erythrophagocytosis (Jang et al., 2011). In addition, a higher level of Pb in serum appears to reduce iron absorption and increase the risk of anemia in children (J.W. Chen et al., 2015). Since hematopoiesis is an iron-dependent process, it can be assumed that the Pb poisoning may interfere with iron absorption. However, the associated mechanisms are still unclear thus far. So-Youn Kwon and colleagues reported that long-term Pb exposure resulted in accumulation of iron in the kidney (Kwon et al., 2015), where Pb further induced the generation of ROS (Fraga and Oteiza, 2002; Valko et al., 2005) and subsequent lipid peroxidation (Zager et al., 2002) and renal fibrosis (Kovtunovych et al., 2010). Besides normocytic anemia described above, secondary porphyria has also been observed as a result of Pb poisoning (Wolf et al., 2001).

3.4. Mercury (Hg)

Due to its widespread applications in fossil fuels and agricultural products, exposure to and potential risk of Hg to human health have raised great concerns in the public (Fang and Chen, 2010; Wu et al., 2013). It has been reported that Hg poisoning can result in nephrotic syndrome (Kazantzis et al., 1962; Munck and Nissen, 1956; Soo et al., 2003; Tang et al., 2006), and aplastic anemia (Priya et al., 2012; Ryrje et al., 1970). However, the adverse effects of Hg on iron metabolism have rarely been studied. A study by Zabinski and colleagues showed that the levels of serum ferritin and other iron status indicators were higher in workers from a Hg manufacturing facility than those in the general population (Zabinski et al., 2000). E. Bárány and colleagues found that the levels of serum Hg and serum ferritin showed a positive correlation-dependent manner (Bárány et al., 2005), whereas the levels of Hg and sTfR/S-Ft (the ratio of soluble TfR in serum and serum ferritin) appeared to have a negative correlation (Bárány et al., 2005). Conversely, af Geijersstam and colleagues reported a reverse phenomenon between plasma-Hg and serum ferritin on exposure to a single amount of Hg-amalgam (af Geijersstam et al., 2001). Yet, no effect has been recognized on iron absorption upon *in vitro* Hg exposure (Iturri and Nuñez, 1998). Therefore, the correlation between Hg exposure and iron metabolism is still controversial, and needs to be further investigated.

3.5. Arsenic (As)

The probable route for human daily exposure to low levels of As is largely from drinking water. The health effects of As exposure are an increasing concern all over the world. Chronic exposure to As may cause skin lesions/cancers, neurological, respiratory, cardiovascular and developmental distress (Naujokas et al., 2013). The molecular mechanisms underlying As-induced adverse effects can be attributed to its binding to sulfur-containing proteins and inactivating more than 200 enzymes (Tchounwou et al., 2012). For example, pyruvate dehydrogenase (PDH), one of the enzymes that can be inhibited by As, catalyzes the reaction of pyruvate to acetyl-CoA and provides the mitochondria with reducing equivalents for electron transport (Shen et al., 2013a). Emerging evidence suggests that inactivation of this enzyme causes the disruption of energy homeostasis (Shen et al., 2013a) and possibly iron homeostasis (Ye and Rouault, 2010). DNA repair enzymes

that mediate nucleotide excision repair (NER) can also be inhibited by As through several pathways, including the induction of nitric oxide (NO) (Shen et al., 2013b). It is considered that NO interacts with the iron center of IRPs, and thus alters the ferritin and transferrin levels, resulting in enlarged cellular LIP (Verma et al., 2015). Moreover, during its metabolism in the body, As needs to be methylated to monomethylarsonic acid (MMA) and dimethyl arsenic acid (DMA) with a methyl group from S-adenosylmethionine (SAM), which is also a substrate for DNA methyltransferase (DNMT). Thus, As exposure has the potential to induce hypomethylation of the genome, causing detrimental effects on human health (Chen et al., 2004; Okoji et al., 2002). Additionally, it has been reported that chronic exposure to As may disturb the balance of trace metals, such as iron, selenium, chromium and Cu. Previous data demonstrated that As exposure could reduce the level of iron in the brain of mice through suppression of iron absorption (Paul et al., 2002; X.X. Wang et al., 2013b).

3.6. Copper (Cu)

Cu is also an essential trace metal element, which, like iron, can transfer electrons. Because of its catalytic function, Cu participates in various physiological activities. Meanwhile, disordered Cu metabolism exerts adverse health effects on humans. In fact, the interaction between Cu and iron has been acknowledged for many years (Fox, 2003; Sharp, 2004). It was recognized that three multi-copper oxidases, ceruloplasmin, hephaestin and zyklopen are involved in the regulation of iron homeostasis (Prohaska, 2011). Ceruloplasmin oxidizes ferrous iron to ferric, a process which is important for iron uptake and storage (Osaki et al., 1966). The role of hephaestin as oxidase is to facilitate the binding of iron and apotransferrin (Donovan et al., 2005). Additionally, there are studies indicating that zyklopen is involved in iron transport in the placenta (Andersen et al., 2007; Wierzbicka and Gromadzka, 2014).

4. Conclusions and perspectives

In this review, we highlight the implications of disordered iron homeostasis in environmental pollutant-induced health effects. Increasing evidence suggests that environmental pollutants could give rise to the disruption of iron metabolism, associated with enhanced cytotoxicity. In the meantime, the disruption of iron homeostasis causes oxidative stress, alters cell growth rates, and thus induces various diseases, including cancers. Therefore, disordered iron homeostasis plays an important role in environmental pollutant-induced adverse effects on humans.

The understanding of the relationship between iron biology and environmental pollutants is still limited, and quite a few questions remain to be answered in the future. For example, previous studies have demonstrated that a variety of environmental pollutants could cause the genetic mutation or functional disability of p53 (Anetor, 2012; Besaratinia and Pfeifer, 2010; Peltonen et al., 2010), which is a most important tumor suppressor. Our preliminary data also identified a crucial role of iron in stabilizing p53 via an interaction with ferritin. This suggests a possible link between pollutant-conducted p53 variations and iron status, and also implies a potential role of

iron in pollutant-triggered DNA damage. Taken together, more efforts are necessary devoted to elaborating the disruptive effects of environmental pollutants on iron homeostasis and associated health risks.

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REFERENCES

- Abiko, Y., Shinkai, Y., Sumi, D., Kumagai, Y., 2010. Reduction of arsenic-induced cytotoxicity through Nrf2/HO-1 signaling in HepG2 cells. *J. Toxicol. Sci.* 35 (3), 419–423.
- af Geijerstam, E., Sandborgh-Englund, G., Jonsson, F., Ekstrand, J., 2001. Mercury uptake and kinetics after ingestion of dental amalgam. *J. Dent. Res.* 80 (9), 1793–1796.
- Agarwal, S., Zaman, T., Tuzcu, E.M., Kapadia, S.R., 2011. Heavy metals and cardiovascular disease: results from the National Health and Nutrition Examination Survey (NHANES) 1999–2006. *Angiology* 62 (5), 422–429.
- Alexander, B.H., Checkoway, H., Costa-Mallen, P., Faustman, E.M., Woods, J.S., Kelsey, K.T., et al., 1998. Interaction of blood lead and delta-aminolevulinic acid dehydratase genotype on markers of heme synthesis and sperm production in lead smelter workers. *Environ. Health Perspect.* 106 (4), 213–216.
- Andersen, H.S., Gambling, L., Holtrop, G., McArdle, H.J., 2007. Effect of dietary copper deficiency on iron metabolism in the pregnant rat. *Br. J. Nutr.* 97 (2), 239–246.
- Anetor, J.I., 2012. Rising environmental cadmium levels in developing countries: threat to genome stability and health. *Niger. J. Physiol. Sci.* 27 (2), 103–115.
- Bárány, E., Bergdahl, I.A., Bratteby, L.E., Lundh, T., Samuelson, G., Skerfving, S., et al., 2005. Iron status influences trace element levels in human blood and serum. *Environ. Res.* 98 (2), 215–223.
- Besaratinia, A., Pfeifer, G.P., 2010. Applications of the human p53 knock-in (Hupki) mouse model for human carcinogen testing. *FASEB J.* 24 (8), 2612–2619.
- Bystrom, L.M., Guzman, M.L., Rivella, S., 2014. Iron and reactive oxygen species: friends or foes of cancer cells? *Antioxid. Redox Signal.* 20 (12), 1917–1924.
- Casals-Casas, C., Desvergne, B., 2011. Endocrine disruptors: from endocrine to metabolic disruption. *Annu. Rev. Physiol.* 73, 135–162.
- Casati, L., Sendra, R., Poletti, A., Negri-Cesi, P., Celotti, F., 2013. Androgen receptor activation by polychlorinated biphenyls: epigenetic effects mediated by the histone demethylase Jarid1b. *Epigenetics* 8 (10), 1061–1068.
- Chen, H., Li, S., Liu, J., Diwan, B.A., Barrett, J.C., Waalkes, M.P., 2004. Chronic inorganic arsenic exposure induces hepatic global and individual gene hypomethylation: implications for arsenic hepatocarcinogenesis. *Carcinogenesis* 25 (9), 1779–1786.
- Chen, A., Kim, S.S., Chung, E., Dietrich, K.N., 2013. Thyroid hormones in relation to lead, mercury, and cadmium exposure in the National Health and Nutrition Examination Survey, 2007–2008. *Environ. Health Perspect.* 121 (2), 181–186.
- Chen, J.W., Li, M.Y., Lv, Q., Chen, G.L., Li, Y., Li, S.J., et al., 2015a. Blood lead level and its relationship to essential elements in preschool children from Nanning, China. *J. Trace Elem. Med. Biol.* 30, 137–141.

- Chen, Y., Zhang, S.P., Wang, X.Y., Guo, W.L., Wang, L., Zhang, D.Q., et al., 2015b. Disordered signaling governing ferroportin transcription favors breast cancer growth. *Cell. Signal.* 27 (1), 168–176.
- Davies, K., 2006. Strategies for eliminating and reducing persistent bioaccumulative toxic substances: common approaches, emerging trends, and level of success. *J. Environ. Health* 69 (5), 9–15 (36, 38).
- Dizdaroglu, M., Rao, G., Halliwell, B., Gajewski, E., 1991. Damage to the DNA bases in mammalian chromatin by hydrogen peroxide in the presence of ferric and cupric ions. *Arch. Biochem. Biophys.* 285 (2), 317–324.
- Donovan, A., Lima, C.A., Pinkus, J.L., Pinkus, G.S., Zon, L.I., Robine, S., et al., 2005. The iron exporter ferroportin/Slc40a1 is essential for iron homeostasis. *Cell Metab.* 1 (3), 191–200.
- Duce, J.A., Tsatsanis, A., Cater, M.A., James, S.A., Robb, E., Wikhe, K., et al., 2010. Iron-export ferroxidase activity of β -amyloid precursor protein is inhibited by zinc in Alzheimer's disease. *Cell* 142 (6), 857–867.
- Elbirt, K.K., Bonkovsky, H.L., 1999. Heme oxygenase: recent advances in understanding its regulation and role. *Proc. Assoc. Am. Physicians* 111 (5), 438–447.
- Fang, T.H., Chen, R.Y., 2010. Mercury contamination and accumulation in sediments of the East China Sea. *J. Environ. Sci.* 22 (8), 1164–1170.
- Farina, M., Avila, D.S., da Rocha, J.B.T., Aschner, M., 2013. Metals, oxidative stress and neurodegeneration: a focus on iron, manganese and mercury. *Neurochem. Int.* 62 (5), 575–594.
- Fox, P.L., 2003. The copper-iron chronicles: the story of an intimate relationship. *Biometals* 16 (1), 9–40.
- Fraga, C.G., Oteiza, P.I., 2002. Iron toxicity and antioxidant nutrients. *Toxicology* 180 (1), 23–32.
- Ganeshaguru, K., Hoffbrand, A.V., Grady, R.W., Cerami, A., 1980. Effect of various iron chelating agents on DNA synthesis in human cells. *Biochem. Pharmacol.* 29 (9), 1275–1279.
- Ganz, T., 2013. Systemic iron homeostasis. *Physiol. Rev.* 93 (4), 1721–1741.
- Ganz, T., Nemeth, E., 2011. Hcpidin and disorders of iron metabolism. *Annu. Rev. Med.* 62, 347–360.
- Gebremariam, S.Y., Beutel, M.W., Yonge, D.R., Flury, M., Harsh, J.B., 2012. Adsorption and desorption of chlorpyrifos to soils and sediments. In: Whitacre, D.M. (Ed.), *Reviews of Environmental Contamination and Toxicology*. vol. 215. Springer, New York, pp. 123–175.
- Gena, P., Calamita, G., Guggino, W.B., 2010. Cadmium impairs albumin reabsorption by down-regulating megalin and ClC5 channels in renal proximal tubule cells. *Environ. Health Perspect.* 118 (11), 1551–1556.
- Gunshin, H., Mackenzie, B., Berger, U.V., Gunshin, Y., Romero, M.F., Boron, W.F., et al., 1997. Cloning and characterization of a mammalian proton-coupled metal-ion transporter. *Nature* 388 (6641), 482–488.
- Hamilton, D.L., Valberg, L.S., 1974. Relationship between cadmium and iron absorption. *Am. J. Physiol.* 227 (5), 1033–1037.
- Han, O., Wessling-Resnick, M., 2002. Copper repletion enhances apical iron uptake and transepithelial iron transport by Caco-2 cells. *Am. J. Physiol. Gastrointest. Liver Physiol.* 282 (3), G527–G533.
- Horiguchi, H., 2007. Anemia induced by cadmium intoxication. *Nihon Eiseigaku Zasshi* 62 (3), 888–904.
- Horiguchi, H., Teranishi, H., Niiya, K., Aoshima, K., Katoh, T., Sakuragawa, N., et al., 1994. Hypoproduction of erythropoietin contributes to anemia in chronic cadmium intoxication: clinical study on itai-itai disease in Japan. *Arch. Toxicol.* 68 (10), 632–636.
- Horiguchi, H., Aoshima, K., Oguma, E., Sasaki, S., Miyamoto, K., Hosoi, Y., et al., 2010. Latest status of cadmium accumulation and its effects on kidneys, bone, and erythropoiesis in inhabitants of the formerly cadmium-polluted Jinzu River Basin in Toyama, Japan, after restoration of rice paddies. *Int. Arch. Occup. Environ. Health* 83 (8), 953–970.
- Horiguchi, H., Oguma, E., Kayama, F., 2011. Cadmium induces anemia through interdependent progress of hemolysis, body iron accumulation, and insufficient erythropoietin production in rats. *Toxicol. Sci.* 122 (1), 198–210.
- Hou, L., Zhang, X., Wang, D., Baccarelli, A., 2012. Environmental chemical exposures and human epigenetics. *Int. J. Epidemiol.* 41 (1), 79–105.
- Huang, B.W., Ray, P.D., Iwasaki, K., Tsuji, Y., 2013. Transcriptional regulation of the human ferritin gene by coordinated regulation of Nrf2 and protein arginine methyltransferases PRMT1 and PRMT4. *FASEB J.* 27 (9), 3763–3774.
- Hunt, K.M., Srivastava, R.K., Elmets, C.A., Athar, M., 2014. The mechanistic basis of arsenicosis: pathogenesis of skin cancer. *Cancer Lett.* 354 (2), 211–219.
- Inoue, S., Kawanishi, S., 1987. Hydroxyl radical production and human DNA damage induced by ferric nitrilotriacetate and hydrogen peroxide. *Cancer Res.* 47 (24 Pt 1), 6522–6527.
- Issaragrisil, S., Kaufman, D.W., Anderson, T., Chansung, K., Leaverton, P.E., Shapiro, S., et al., 2006. The epidemiology of aplastic anemia in Thailand. *Blood* 107 (4), 1299–1307.
- Iturri, S., Nuñez, M.T., 1998. Effect of copper, cadmium, mercury, manganese and lead on Fe^{2+} and Fe^{3+} absorption in perfused mouse intestine. *Digestion* 59 (6), 671–675.
- Jang, W.H., Lim, K.M., Kim, K., Noh, J.Y., Kang, S., Chang, Y.K., et al., 2011. Low level of lead can induce phosphatidylserine exposure and erythrophagocytosis: a new mechanism underlying lead-associated anemia. *Toxicol. Sci.* 122 (1), 177–184.
- Järup, L., 2003. Hazards of heavy metal contamination. *Br. Med. Bull.* 68 (1), 167–182.
- Kazantzis, G., Schiller, K.F., Asscher, A.W., Drew, R.G., 1962. Albuminuria and the nephrotic syndrome following exposure to mercury and its compounds. *Q. J. Med.* 31, 403–418.
- Khan, K., Lu, Y., Khan, H., Zakir, S., Ihsanullah, Khan, S., et al., 2013. Health risks associated with heavy metals in the drinking water of Swat, northern Pakistan. *J. Environ. Sci.* 25 (10), 2003–2013.
- Kim, N.H., Hyun, Y.Y., Lee, K.B., Chang, Y., Rhu, S., Oh, K.H., et al., 2015. Environmental heavy metal exposure and chronic kidney disease in the general population. *J. Korean Med. Sci.* 30 (3), 272–277.
- Kodavanti, P.R., Tilson, H.A., 1997. Structure-activity relationships of potentially neurotoxic PCB congeners in the rat. *Neurotoxicology* 18 (2), 425–441.
- Koedrich, P., Seo, Y.R., 2011. Advances in carcinogenic metal toxicity and potential molecular markers. *Int. J. Mol. Sci.* 12 (12), 9576–9595.
- Koji, N., Ryumon, H., Yuichi, Y., Teruhiko, K., Ikiko, T., Masao, I., 1984. Iron concentrations in liver and kidney of cadmium-exposed human subjects. *Toxicol. Lett.* 21 (2), 209–212.
- Kovtunovych, G., Eckhaus, M.A., Ghosh, M.C., Ollivierre-Wilson, H., Rouault, T.A., 2010. Dysfunction of the heme recycling system in heme oxygenase 1-deficient mice: effects on macrophage viability and tissue iron distribution. *Blood* 116 (26), 6054–6062.
- Kunimoto, M., Miura, T., Kubota, K., 1985. An apparent acceleration of age-related changes of rat red blood cells by cadmium. *Toxicol. Appl. Pharmacol.* 77 (3), 451–457.
- Kwon, S.Y., Bae, O.N., Noh, J.Y., Kim, K., Kang, S., Shin, Y.J., et al., 2015. Erythrophagocytosis of lead-exposed erythrocytes by renal tubular cells: possible role in lead-induced nephrotoxicity. *Environ. Health Perspect.* 123 (2), 120–127.
- Lachant, N.A., Tomoda, A., Tanaka, K.R., 1984. Inhibition of the pentose phosphate shunt by lead: a potential mechanism for hemolysis in lead poisoning. *Blood* 63 (3), 518–524.
- Lee, D.W., Gelein, R.M., Opanashuk, L.A., 2006. Heme-oxygenase-1 promotes polychlorinated biphenyl mixture aroclor

- 1254-induced oxidative stress and dopaminergic cell injury. *Toxicol. Sci.* 90 (1), 159–167.
- Li, Q., Chen, H., Huang, X., Costa, M., 2006a. Effects of 12 metal ions on iron regulatory protein 1 (IRP-1) and hypoxia-inducible factor-1 α (HIF-1 α) and HIF-regulated genes. *Toxicol. Appl. Pharmacol.* 213 (3), 245–255.
- Li, Y., Wang, Y.B., Gou, X., Su, Y.B., Wang, G., 2006b. Risk assessment of heavy metals in soils and vegetables around non-ferrous metals mining and smelting sites, Baiyin, China. *J. Environ. Sci.* 18 (6), 1124–1134.
- Li, B., Li, X., Zhu, B., Zhang, X.Y., Wang, Y., Xu, Y.Y., et al., 2013. Sodium arsenite induced reactive oxygen species generation, nuclear factor (erythroid-2 related) factor 2 activation, heme oxygenase-1 expression, and glutathione elevation in Chang human hepatocytes. *Environ. Toxicol.* 28 (7), 401–410.
- Lioy, P.J., Rappaport, S.M., 2011. Exposure science and the exposome: an opportunity for coherence in the environmental health sciences. *Environ. Health Perspect.* 119 (11), A466–A467.
- Lucena, R.A., Allam, M.F., Costabeber, I.H., Villarejo, M.L., Navajas, R.F., 2001. Breast cancer risk factors: PCB congeners. *Eur. J. Cancer Prev.* 10 (1), 117–119.
- Mason, L.H., Harp, J.P., Han, D.Y., 2014. Pb neurotoxicity: neuropsychological effects of lead toxicity. *BioMed Res. Int.* <http://dx.doi.org/10.1155/2014/840547> (ID: 840547).
- Mink, P.J., Kimmel, C.A., Li, A.A., 2012. Potential effects of chlorpyrifos on fetal growth outcomes: implications for risk assessment. *J. Toxicol. Environ. Health B Crit. Rev.* 15 (4), 281–316.
- Moore, M.R., Goldberg, A., Yeung-Laiwah, A.A.C., 1987. Lead effects on the heme biosynthetic pathway. Relationship to toxicity. *Ann. N. Y. Acad. Sci.* 514, 191–203.
- Munck, O., Nissen, N.I., 1956. Development of nephrotic syndrome during treatment with mercurial diuretics. *Acta Med. Scand.* 153 (4), 307–313.
- Naujokas, M.F., Anderson, B., Ahsan, H., Aposhian, H.V., Graziano, J.H., Thompson, C., et al., 2013. The broad scope of health effects from chronic arsenic exposure: update on a worldwide public health problem. *Environ. Health Perspect.* 121 (3), 295–302.
- Okoji, R.S., Yu, R.C., Maronpot, R.R., Froines, J.R., 2002. Sodium arsenite administration via drinking water increases genome-wide and Ha-ras DNA hypomethylation in methyl-deficient C57BL/6J mice. *Carcinogenesis* 23 (5), 777–785.
- Osaki, S., Johnson, D.A., Frieden, E., 1966. The possible significance of the ferrous oxidase activity of ceruloplasmin in normal human serum. *J. Biol. Chem.* 241 (12), 2746–2751.
- Osborne, N.J., Gurrin, L.C., Allen, K.J., Constantine, C.C., Delatycki, M.B., McLaren, C.E., et al., 2010. HFE C282Y homozygotes are at increased risk of breast and colorectal cancer. *Hepatology* 51 (4), 1311–1318.
- Oskarsson, A., Fowler, B.A., 1985. Effects of lead on the heme biosynthetic pathway in rat kidney. *Exp. Mol. Pathol.* 43 (3), 409–417.
- Park, B.Y., Chung, J., 2009. Cadmium increases ferroportin-1 gene expression in J774 macrophage cells via the production of reactive oxygen species. *Nutr. Res. Pract.* 3 (3), 192–199.
- Pasricha, S.R., Drakesmith, H., Black, J., Hipgrave, D., Biggs, B.A., 2013. Control of iron deficiency anemia in low- and middle-income countries. *Blood* 121 (14), 2607–2617.
- Paul, P.C., Misbahuddin, M., Ahmed, A.N.N., Dewan, Z.F., Mannan, M.A., 2002. Accumulation of arsenic in tissues of iron-deficient rats. *Toxicol. Lett.* 135 (3), 193–197.
- Peltonen, J.K., Helppe, H.M., Pääkkö, P., Turpeenniemi-Hujanen, T., Vahakangas, K.H., 2010. p53 in head and neck cancer: functional consequences and environmental implications of TP53 mutations. *Head Neck Oncol.* 2, 36.
- Porta, M., 2006. Persistent organic pollutants and the burden of diabetes. *Lancet* 368 (9535), 558–559.
- Priya, N., Nagaprabhu, V.N., Kurian, G., Seethalakshmi, N., Rao, G.G., Unni, V.N., 2012. Aplastic anemia and membranous nephropathy induced by intravenous mercury. *Indian J. Nephrol.* 22 (6), 451–454.
- Prohaska, J.R., 2011. Impact of copper limitation on expression and function of multicopper oxidases (ferroxidases). *Adv. Nutr.* 2 (2), 89–95.
- Qian, Y., Zhang, S., Guo, W., Ma, J., Chen, Y., Wang, L., et al., 2015. Polychlorinated biphenyls (PCBs) inhibit hepcidin expression through an estrogen-like effect associated with disordered systemic iron homeostasis. *Chem. Res. Toxicol.* 28 (4), 629–640.
- Reaves, D.K., Ginsburg, E., Bang, J.J., Fleming, J.M., 2015. Persistent organic pollutants and obesity: are they potential mechanisms for breast cancer promotion? *Endocr. Relat. Cancer* 22 (2), R69–R86.
- Richardson, D.R., Kalinowski, D.S., Lau, S., Jansson, P.J., Lovejoy, D.B., 2009. Cancer cell iron metabolism and the development of potent iron chelators as anti-tumour agents. *Biochim. Biophys. Acta* 1790 (7), 702–717.
- Ridano, M.E., Racca, A.C., Flores-Martin, J., Camolotto, S.A., de Potas, G.M., Genti-Raimondi, S., et al., 2012. Chlorpyrifos modifies the expression of genes involved in human placental function. *Reprod. Toxicol.* 33 (3), 331–338.
- Rokadia, H.K., Agarwal, S., 2013. Serum heavy metals and obstructive lung disease: results from the National Health and Nutrition Examination Survey. *Chest* 143 (2), 388–397.
- Ryrie, D.R., Toghiani, P.J., Tanna, M.K., Galan, G.N., 1970. Marrow suppression from mercury poisoning? *Br. Med. J.* 1 (5694), 499.
- Santamaria, R., Fiorito, F., Irace, C., De Martino, L., Maffettone, C., Granato, G.E., et al., 2011. 2,3,7,8-Tetrachlorodibenzo-*p*-dioxin impairs iron homeostasis by modulating iron-related proteins expression and increasing the labile iron pool in mammalian cells. *Biochim. Biophys. Acta* 1813 (5), 704–712.
- Satarug, S., Garrett, S.H., Sens, M.A., Sens, D.A., 2010. Cadmium, environmental exposure, and health outcomes. *Environ. Health Perspect.* 118 (2), 182–190.
- Sato, M., Kondoh, M., 2002. Recent studies on metallothionein: protection against toxicity of heavy metals and oxygen free radicals. *Tohoku J. Exp. Med.* 196 (1), 9–22.
- Sha, J.J., Wang, Y., Lv, J.X., Wang, H., Chen, H.M., Qi, L.L., et al., 2015. Effects of two polybrominated diphenyl ethers (BDE-47, BDE-209) on the swimming behavior, population growth and reproduction of the rotifer *Brachionus plicatilis*. *J. Environ. Sci.* 28, 54–63.
- Sharp, P., 2004. The molecular basis of copper and iron interactions. *Proc. Nutr. Soc.* 63 (4), 563–569.
- Shen, S.W., Li, X.F., Cullen, W.R., Weinfeld, M., Le, X.C., 2013a. Arsenic binding to proteins. *Chem. Rev.* 113 (10), 7769–7792.
- Shen, S.W., Wang, C., Weinfeld, M., Le, X.C., 2013b. Inhibition of nucleotide excision repair by arsenic. *Chin. Sci. Bull.* 58 (2), 214–221.
- Singh, B.K., Walker, A., Wright, D.J., 2002. Persistence of chlorpyrifos, fenamiphos, chlorothalonil, and pendimethalin in soil and their effects on soil microbial characteristics. *Bull. Environ. Contam. Toxicol.* 69 (2), 181–188.
- Singh, S., Kumar, V., Thakur, S., Banerjee, B.D., Chandna, S., Rautela, R.S., et al., 2011. DNA damage and cholinesterase activity in occupational workers exposed to pesticides. *Environ. Toxicol. Pharmacol.* 31 (2), 278–285.
- Smialowicz, R.J., Andrews, J.E., Riddle, M.M., Rogers, R.R., Luebke, R.W., Copeland, C.B., 1989. Evaluation of the immunotoxicity of low level PCB exposure in the rat. *Toxicology* 56 (2), 197–211.
- Smith, A.G., Carthew, P., Clothier, B., Constantin, D., Francis, J.E., Madra, S., 1995. Synergy of iron in the toxicity and carcinogenicity of polychlorinated biphenyls (PCBs) and related chemicals. *Toxicol. Lett.* 82–83, 945–950.
- Solenkova, N.V., Newman, J.D., Berger, J.S., Thurston, G., Hochman, J.S., Lamas, G.A., 2014. Metal pollutants and cardiovascular disease: mechanisms and consequences of exposure. *Am. Heart J.* 168 (6), 812–822.

- Soo, Y.O.Y., Chow, K.M., Lam, C.W.K., Lai, F.M.M., Szeto, C.C., Chan, M.H.M., et al., 2003. A whitened face woman with nephrotic syndrome. *Am. J. Kidney Dis.* 41 (1), 250–253.
- Sorg, O., 2014. AhR signalling and dioxin toxicity. *Toxicol. Lett.* 230 (2), 225–233.
- Staessen, J.A., Roels, H.A., Emelianov, D., Kuznetsova, T., Thijs, L., Vangronsveld, J., et al., 1999. Environmental exposure to cadmium, forearm bone density, and risk of fractures: prospective population study. *Public Health and Environmental Exposure to Cadmium (PheeCad) Study Group. Lancet* 353 (9159), 1140–1144.
- Stonard, M.D., Webb, M., 1976. Influence of dietary cadmium on the distribution of the essential metals copper, zinc and iron in tissues of the rat. *Chem. Biol. Interact.* 15 (4), 349–363.
- Sun, L., Zhang, S.P., Guo, W.L., He, W., Qian, Y., Qu, G.B., et al., 2014. Sublethal exposure of organophosphate pesticide chlorpyrifos alters cellular iron metabolism in hepatocytes and macrophages. *Int. J. Mol. Med.* 34 (5), 1395–1400.
- Sun, L., Wang, L.X., Wang, Z., He, W., Zhang, S.P., Guo, W.L., et al., 2015. Cadmium depletes cellular iron availability through enhancing ferroportin translation via iron responsive element. *Mol. Med. Rep.* 11 (4), 3129–3133.
- Tang, H.L., Chu, K.H., Mak, Y.F., Lee, W., Cheuk, A., Yim, K.F., et al., 2006. Minimal change disease following exposure to mercury-containing skin lightening cream. *Hong Kong Med. J.* 12 (4), 316–318.
- Tchounwou, P.B., Yedjou, C.G., Patlolla, A.K., Sutton, D.J., 2012. Heavy metal toxicity and the environment. *EXS* 101, 133–164.
- Thomas, L.D., Hodgson, S., Nieuwenhuijsen, M., Jarup, L., 2009. Early kidney damage in a population exposed to cadmium and other heavy metals. *Environ. Health Perspect.* 117 (2), 181–184.
- Tomita, M., Yoshida, T., Fukumori, J., Yamaguchi, S., Kojima, S., Fukuyama, T., et al., 2013. *p,p'*-DDT induces microcytic anemia in rats. *J. Toxicol. Sci.* 38 (5), 775–782.
- Torti, S.V., Torti, F.M., 2011. Ironing out cancer. *Cancer Res.* 71 (5), 1511–1514.
- Torti, S.V., Torti, F.M., 2013. Iron and cancer: more ore to be mined. *Nat. Rev. Cancer* 13 (5), 342–355.
- Turusov, V., Rakitsky, V., Tomatis, L., 2002. Dichlorodiphenyltrichloroethane (DDT): ubiquity, persistence, and risks. *Environ. Health Perspect.* 110 (2), 125–128.
- Vaiserman, A., 2014. Early-life exposure to endocrine disrupting chemicals and later-life health outcomes: an epigenetic bridge? *Aging Dis.* 5 (6), 419–429.
- Valentine, W.N., Paglia, D.E., Fink, K., Madokoro, G., 1976. Lead poisoning: association with hemolytic anemia, basophilic stippling, erythrocyte pyrimidine 5'-nucleotidase deficiency, and intraerythrocytic accumulation of pyrimidines. *J. Clin. Invest.* 58 (4), 926–932.
- Valko, M., Morris, H., Cronin, M.T.D., 2005. Metals, toxicity and oxidative stress. *Curr. Med. Chem.* 12 (10), 1161–1208.
- Verma, N., Pink, M., Petrat, F., Rettenmeier, A.W., Schmitz-Spanke, S., 2015. Proteomic analysis of human bladder epithelial cells by 2D blue native SDS-PAGE reveals TCDD-induced alterations of calcium and iron homeostasis possibly mediated by nitric oxide. *J. Proteome Res.* 14 (1), 202–213.
- Vested, A., Giwercman, A., Bonde, J.P., Toft, G., 2014. Persistent organic pollutants and male reproductive health. *Asian J. Androl.* 16 (1), 71–80.
- Wang, X., Ren, N.Q., Qi, H., Ma, W.L., Li, Y.F., 2009. Levels, distributions, and source identification of organochlorine pesticides in the topsoils in Northeastern China. *J. Environ. Sci.* 21 (10), 1386–1392.
- Wang, L., Zhang, S.P., Lin, R.H., Li, L., Zhang, D.Q., Li, X.H., et al., 2013a. PCB-77 disturbs iron homeostasis through regulating hepcidin gene expression. *Gene* 532 (1), 146–151.
- Wang, X.X., Zhang, J., Zhao, L., Hu, S.H., Piao, F.Y., 2013b. Effect of subchronic exposure to arsenic on levels of essential trace elements in mice brain and its gender difference. *BioMetals* 26 (1), 123–131.
- WHO, 2006. Preventing disease through healthy environments: towards an estimate of the environmental burden of disease Available at: http://www.who.int/quantifying_ehimpacts/publications/preventingdisease/en/.
- Whysner, J., Wang, C.X., 2001. Hepatocellular iron accumulation and increased cell proliferation in polychlorinated biphenyl-exposed Sprague–Dawley rats and the development of hepatocarcinogenesis. *Toxicol. Sci.* 62 (1), 36–45.
- Wierzbicka, D., Gromadzka, G., 2014. Ceruloplasmin, hephaestin and cytochrome b5: the three multicopper oxidases important for human iron metabolism. *Postepy Hig. Med. Dosw.* 68, 912–924.
- Wolf, C., Binder, R., Barth, A., Konnaris, C., Rüdiger, H.W., 2001. Chronic anemia and abdominal pain as a sequela of lead poisoning. *Dtsch. Med. Wochenschr.* 126 (19), 556–558.
- Wolff, M.S., Zeleniuch-Jacquotte, A., Dubin, N., Toniolo, P., 2000. Risk of breast cancer and organochlorine exposure. *Cancer Epidemiol. Biomark. Prev.* 9 (3), 271–277.
- Wu, M.Q., Yan, C.H., Xu, J., Wu, W., Li, H., Zhou, X., 2013. Umbilical cord blood mercury levels in China. *J. Environ. Sci.* 25 (2), 386–392.
- Xiong, W., Wang, L., Yu, F., 2014. Regulation of cellular iron metabolism and its implications in lung cancer progression. *Med. Oncol.* 31 (7), 28.
- Yang, Y.B., Liu, Z.T., Zheng, M.H., Zhao, Y.Y., Wang, L., Sun, W., et al., 2008. The acute lethality and endocrine effect of 1,2,3,7,8-PeCDD in juvenile goldfish (*Carassius auratus*) in vivo. *J. Environ. Sci.* 20 (2), 240–245.
- Ye, H., Rouault, T.A., 2010. Erythropoiesis and iron sulfur cluster biogenesis. *Adv. Hematol.* 2010. <http://dx.doi.org/10.1155/2010/329394>.
- Yu, R.A., He, L.F., Chen, X.M., 2007a. Effects of cadmium on hepatocellular DNA damage, proto-oncogene expression and apoptosis in rats. *Biomed. Environ. Sci.* 20 (2), 146–153.
- Yu, Y., Kovacevic, Z., Richardson, D.R., 2007b. Tuning cell cycle regulation with an iron key. *Cell Cycle* 6 (16), 1982–1994.
- Zabinski, Z., Dabrowski, Z., Moszczynski, P., Rutowski, J., 2000. The activity of erythrocyte enzymes and basic indices of peripheral blood erythrocytes from workers chronically exposed to mercury vapours. *Toxicol. Ind. Health* 16 (2), 58–64.
- Zager, R.A., Johnson, A.C.M., Hanson, S.Y., Wasse, H., 2002. Parenteral iron formulations: a comparative toxicologic analysis and mechanisms of cell injury. *Am. J. Kidney Dis.* 40 (1), 90–103.
- Zhang, J., Piantadosi, C.A., 1992. Mitochondrial oxidative stress after carbonmonoxide hypoxia in the rat brain. *J. Clin. Invest.* 90 (4), 1193–1199.
- Zhang, C., Zhang, F., 2015. Iron homeostasis and tumorigenesis: molecular mechanisms and therapeutic opportunities. *Protein Cell* 6 (2), 88–100.
- Zhang, S., Chen, Y., Guo, W., Yuan, L., Zhang, D., Xu, Y., et al., 2014. Disordered hepcidin-ferroportin signaling promotes breast cancer growth. *Cell. Signal.* 26 (11), 2539–2550.
- Zhao, L., Wang, F., Zhao, J., 2014. Identification and functional characteristics of chlorpyrifos-degrading and plant growth promoting bacterium *Acinetobacter calcoaceticus*. *J. Basic Microbiol.* 54 (5), 457–463.
- Zhou, P., Guo, J., Zhou, X.Y., Zhang, W., Liu, L.L., Liu, Y.C., et al., 2014. PM_{2.5}, PM₁₀ and health risk assessment of heavy metals in a typical printed circuit boards manufacturing workshop. *J. Environ. Sci.* 26 (10), 2018–2026.